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Pulmonary valvular dysplasia
A cardiofacial syndrome

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Four patients with pulmonary valvular dysplasia are described. The primary features of this disorder include clinical and laboratory findings similar to those of pulmonary valvular stenosis but without a pulmonary ejection click, in association with an unusual facies, small stature, and mental retardation. The importance of the recognition of this lesion before operative intervention is stressed. Though chromosomal studies are normal, there is a possibility of aetiological genetic recessive factors. The relation of these patients to previously described cardiofacial syndromes is discussed. Recognition of their similarities may prevent the recurrent 'discovery' of new syndromes based on minor variations of associated anomalies.

A type of right ventricular obstruction with thickening and immobility of the pulmonary valve leaflets has recently been described (Koretzky *et al.*, 1969). In contrast to other forms of pulmonary valvular stenosis syndromes, these cases were characterized by absence of annular hypoplasia and the presence of three distinct valve cusps without commissural fusion. The characteristic thickening of the affected valve cusps prevented their excursion and resulted in obstruction to right ventricular outflow. These features were associated with a high operative mortality, and necessitated variations in the usual surgical approach to this particular type of pulmonary valve obstruction.

The syndrome of pulmonary valvular dysplasia has several distinct features: (1) a pulmonary ejection murmur but no click; (2) unusual facies and physical characteristics (Fig. 1); (3) mental and growth retardation; (4) angiocardiographic or pathological evidence of thickening of the pulmonary valve leaflets without 'doming', consistent with lack of commissural fusion.

Case reports

This report concerns 4 additional patients similar to those previously described (Koretzky *et al.*, 1969). Clinical features are summarized in the Table. The cardiac findings are identical to pulmonary valvular stenosis except for the consistent absence of an ejection click. The chest *x*-ray is similar to that found in pulmonary valvular stenosis as is the electrocardiogram, except that the frontal loop rotated counterclockwise with a superiorly placed mean QRS axis in 2 patients (Fig. 2). Similar findings were reported by Koretzky *et al.* (1969). Cardiac catheterization with right ventriculography is diagnostic (Fig. 3) and associated congenital cardiovascular malformations are common. In one patient (Case 1) the diagnosis was confirmed at operation where the pulmonary valve leaflets were found to be deformed, rolled back, and thickened, but the commissures were essentially completely formed and there was no appreciable fusion or stenosis.

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Discussion

The syndrome of supravalvular aortic stenosis with mental retardation and unusual facies was first described by Williams, Barratt-Boyes, and Lowe (1961), and subsequently over 100 cases have been reported with additional abnormalities including: infantile hypercalcaemia, narrowing of the peripheral systemic and pulmonary arteries, inguinal hernias, strabismus, dentition abnormalities, retinal abnormalities on angiography, and blue irides. Chromosomal studies performed on patients with that syndrome have been normal (Eberle and Beuren, 1963; Joseph, Polani, and Gold, 1963; de Grouchy and Emerit, 1963) with one exception (Palmer, 1963; Merritt *et al.*, 1963).

Hartel, Frick, and Halonen (1968) described a case of supravalvular pulmonary stenosis in a patient with mental retardation and a peculiar facies similar to that seen in the supravalvular aortic stenosis syndrome and suggested that their case might be a variant not previously described. Our patients had

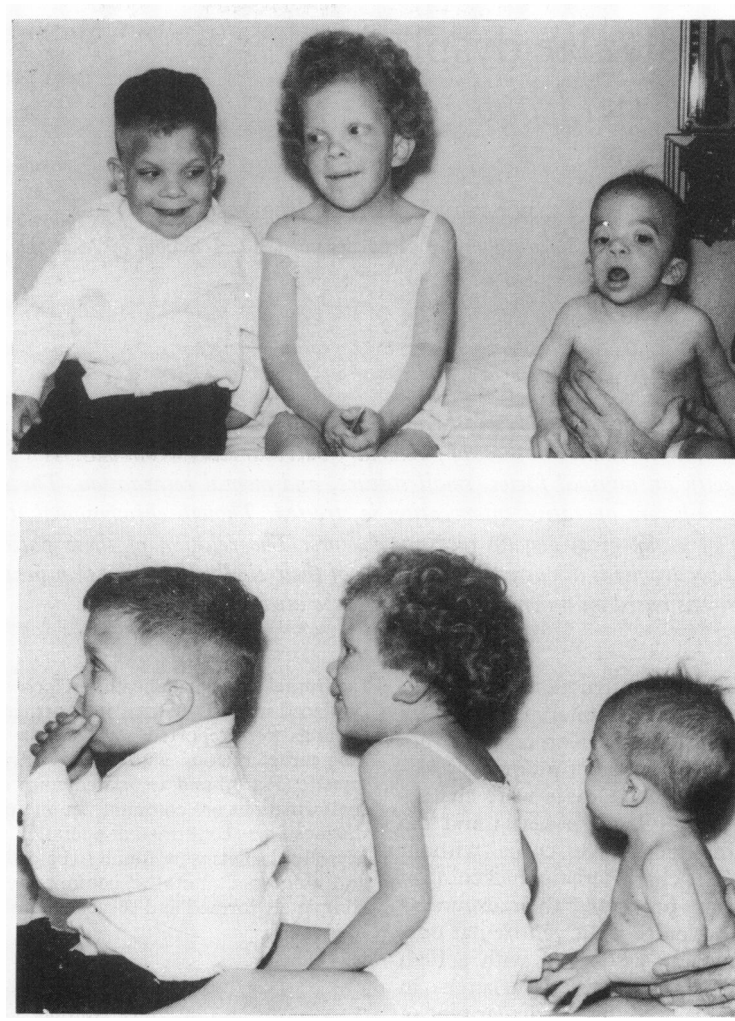

FIG. 1 *Cases 1, 3, and 2 from left to right. Note very similar facies characterized by hypertelorism, epicanthal folds, and low set ears.*

TABLE *Summary of clinical and laboratory findings in 4 patients*

Case No.	*Age (yr)*	*Sex*	*Percentile growth*		*Mental retard.*	*Unusual facies*	*Pulmon. ejection murmur*	*Ejection click*	*Assoc. defect*	*Electrocardiogram*		
			Ht.	*Wt.*						*Axis*	*RV hypertr.*	*RA enlargement*
1	5	M	3rd	3rd	+	+	4/6	—	Atrial septal defect	−100°	+	+
2	2½	M	10th	10th	−	+	4/6	—	Ventric. septal defect; pulm. valvular insufficiency	−100°	+	+
3	12	F	3rd	20th	+	+	3/6	—	—	+120°	+	+
4	5	F	3rd	3rd	+	+	4/6	—	Persistent ductus; pulm. artery stenosis	+160°	+	−

+ = Present; − = Absent. * Pulmonary arteries distal to coarctation.

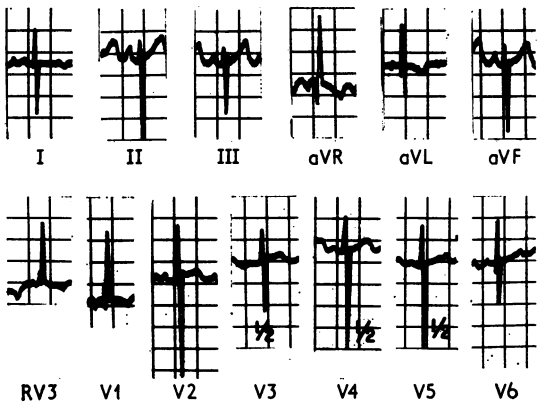

FIG. 2 *Electrocardiogram (Case 1) showing a mean QRS axis of −100°, right ventricular hypertrophy, and right atrial enlargement.*

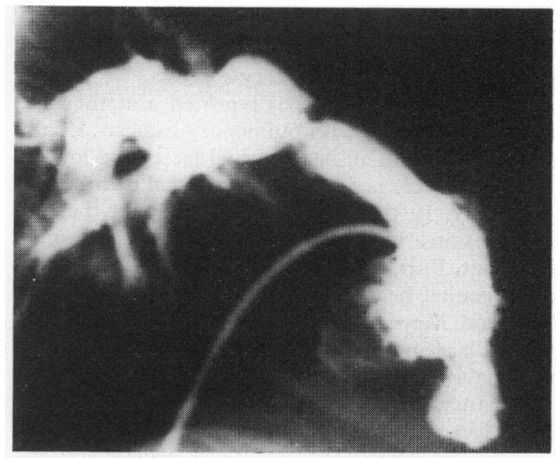

FIG. 3 *Lateral selective right ventricular angiocardiogram (Case 3) in pulmonary valvular dysplasia showing a thickened pulmonary valve without 'doming' and post-stenotic dilatation of the pulmonary trunk.*

facies resembling those described in the previously mentioned reports (Fig. 1) together with mental retardation in 3 of them. The present cases therefore may represent a variant of a cardiofacial syndrome more common than previously expected, and possibly due to a similar but as yet unknown cause.

One of the interesting aspects of this report is the difficulty of differentiation of the various forms of pulmonary valvular obstruction. The associated craniofacial abnormalities indicate a broad but related spectrum of facial abnormality and pulmonary valve pathology and suggest a related gene locus in cases described by Noonan and Ehmke (1963), Noonan (1968), Hartel *et al.* (1968), Koretzky *et al.* (1969), Williams *et al.* (1961), and Hartel *et al.* (1968). Wood (1956) mentioned the hypertelorism and round face of many patients with pulmonary valvular stenosis. Noonan and Ehmke (1963) and Noonan (1968) describe a large series of patients who closely resemble those reported in the paper by Koretzky *et al.* (1969). Noonan's patients had hypertelorism, short neck, low set ears, curly hair, and mental and growth retardation. In contrast to ours, her patients had micrognathia and a very high incidence of chest and other musculoskeletal deformities. A difference of great surgical and prognostic import is based on surgical, pathological, or angiocardiographic proof of pulmonary valve thickening without commissural fusion. In spite of reported minor differences, it seems clear that we are dealing with a spectrum of pulmonary valve deformities of facial and other anatomical abnormalities.

Chromosomal analysis was performed on peripheral blood samples in each of our patients and normal karyotypes were obtained. No minor structural variation was noted when the chromosomes were closely examined for each patient or on comparison of the karyotypes from all patients.

The aetiology of most congenital defects is not known. Except for a few specific syndromes, the genetic contribution to this group of diseases is also poorly defined. In a study of 56 children with pulmonary stenosis, Lamy, de Grouchy, and Schweisguth (1957) suggested that genetic factors might be more important in pulmonary stenosis than in other congenital heart disorders because of the high consanguinity rate and familial incidence as well as the low frequency of irregularities during pregnancy. It is not clear in their cases how frequently the cardiac abnormality was associated with unusual facies. Campbell (1954) reviewed 125 cases of pulmonary stenosis and found an incidence of noncardiac malformation of 13 per cent. Though none of his

Angiograms		*Catheterization data*		*Karyotype*
Thickened pulm. valve	*Commissural fusion*	*Rt. ventricle*	*Pulm. valve*	
+	−	87	?	Normal
+	−	50	22	Normal
+	−	60	12	Normal
+	−	100	15*	Normal

patients was noted to have characteristic facies, he also concluded that genetic factors might have an aetiological role in pulmonary stenosis.

Koroxenidis *et al.* (1966) reported a mother and 4 of her 8 children with pulmonary stenosis. Of the affected children, all had unusual facies and low set ears which were not seen in the normal members of the family. In this family, it was thought that the heart lesions were transmitted as an autosomal dominant. Further suggestion of a genetic aetiology in congenital heart disease comes from reports by Nora and Meyer (1966) and Nora *et al.* (1967) in which a large number of families and a large number of twins were evaluated.

Intrauterine viral infections such as rubella may also affect the development of the cardiovascular system. The heterogeneity of these genetic and environmental factors can lead to some confusion because different combinations may lead to the same congenital malformation. Studies in our patients failed to define a specific and definite genetic aetiological factor. The similarity of the clinical findings in conditions mentioned above does nevertheless suggest the possibility of a common factor in their aetiology. The negative family histories do not rule out the possibility of genetic recessive factors and though dominant inheritance seems unlikely, it is possible that inheritance plays a role. The normal chromosome studies do not exclude changes, such as partial deletion or inversion, which current techniques cannot detect.

Comment

The importance of preoperative recognition of pulmonary valvular dysplasia must be stressed, because simple valvulotomy will probably afford little relief and the operative mortality is high. If operative therapy is imperative, valve replacement, resection of a valve leaflet, or a patch graft across the annulus should be considered.

The prognosis of these patients is poorer than that of the usual pulmonary valvular stenosis, in view of associated abnormalities and the reported high surgical mortality of 38 per cent (Koretzky *et al.*, 1969). The use of other operative techniques as mentioned above may reduce this surgical mortality, but the child's prognosis for a 'functionally normal' life depends upon the degree of his noncardiovascular abnormalities, namely the growth and mental retardation.

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